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EPISOD puts an end to sphincter of Oddi dysfunction type III

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Title: Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy - the EPISOD randomized clinical trial

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Summary

The Rome III revision of the Milwaukee Biliary Group classification has long been utilized to diagnose, classify and drive intervention in patients with suspected sphincter of Oddi dysfunction (SOD). SOD Type III is defined as recurrent biliary-type pain in the absence of elevated liver enzymes and/or imaging abnormalities (common bile duct <8 mm) [1]. While patients with SOD Type II are more likely to have manometric evidence of SOD (55% of the time), studies have shown that only 28% of patients with SOD Type III have manometric evidence of biliary sphincter dysfunction [2]. In 1989, Geenan *et al* showed that 17 of 18 patients with verified SOD on manometry benefitted from endoscopic sphincterotomy [3]. Subsequent literature from the 1990's revealed that patients with SOD Type I benefit from sphincterotomy without the need for manometry. These studies also showed a poor correlation between the results of manometry and response to sphincterotomy [4-6]. Based on the low rate of manometric changes in SOD Type III as well as the aforementioned poor correlation of sphincter manometry with response to sphincterotomy, the optimal management for these patients remains a therapeutic challenge.

In the May issue of JAMA, Cotton *et al* [7] present a multi-center, prospective, sham-controlled randomized trial demonstrating that endoscopic sphincterotomy did not reduce disability due to pain in patients presenting with abdominal pain (suspected SOD Type III) after cholecystectomy. With over 700,000 patients undergoing cholecystectomy every year [8] and greater than 10% reporting pain afterwards [9], Cotton *et al* set out to identify if patients with SOD Type III

respond to endoscopic sphincterotomy (biliary and/or pancreatic). In addition, the ability of sphincter manometry to predict outcomes was evaluated. The trial was conducted at 7 tertiary centers throughout the US. Between 2008 and 2012, 214 patients (predominantly female) post-cholecystectomy with suspected SOD Type III underwent randomization. All patients underwent ERCP, sphincter manometry and were then randomized, regardless of manometry results, to sphincterotomy (n=141) versus sham sphincterotomy (n=73). Within the sphincterotomy group, patients with pancreatic sphincter hypertension were randomized to biliary versus dual (biliary and pancreatic) sphincterotomy. Both groups received small caliber pancreatic stents but no rectal indomethacin. The treatment was considered successful if the patients had a low RAPID score (<6 days of lost productivity due to pain) at 9 and 12 months, did not require a repeat ERCP, and/or did not require narcotics.

Overall, the investigators found that pain and disability were reduced in both groups during 12-month follow up, yet it was the sham sphincterotomy group (37%; 95%CI 25.9-48.1%) that experienced successful treatment more often than the sphincterotomy group (23%; 95%CI 15.8-29.6%). In patients with pancreatic sphincter hypertension, dual sphincterotomy (30%; 95% CI 16.7-42.9%) was equivalent to biliary sphincterotomy alone (20%; 95% CI 8.7-30.5%). No association was found between outcomes and manometry results. No specific subgroups appeared to benefit from sphincterotomy. Patients in an additional observational arm had the same success rates. Complication rates were reported with pancreatitis occurring in 11% and 15% of the sphincterotomy and sham groups respectively.

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Conflict of Interest: None

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Opinion

The EPISOD trial stands as the most well executed trial in patients with suspected sphincter of Oddi dysfunction to date. Among this study's key strengths is its design. The stringent inclusion/exclusion criteria ensured a specific patient population. Previous studies assessed the effect of sphincterotomy on post-cholecystectomy pain but did not

specifically target patients with SOD type III. Cotton *et al* performed a thorough assessment of psychological status and assessed for the presence of functional gastrointestinal disease at enrollment [10]. While it is known that patients with SOD often carry these comorbid conditions [11], there is no prior literature connecting their presence and the response to endoscopic therapy. The authors were able to firmly establish, as well as disprove a common misconception, that the presence of functional digestive disease does not predict the response to sphincterotomy. Finally, the authors chose objective, comprehensive and clinically relevant definitions of success/failure of the study intervention. They were also able to show that their conclusions remained in *post-hoc* analyses using less stringent definitions. The fact that prior sphincterotomy studies used re-intervention alone as an objective measure of treatment failure may account for previous positive results. It is possible that repeat endoscopic interventions were avoided due to their procedural risks and thus patients who were truly treatment failures were considered to be treatment successes.

There were very few shortcomings to this study. All patients underwent pancreatograms, an uncommon practice unless specifically indicated, during ERCP to rule out pancreas divisum (an exclusion criterion). As well, to reduce the risk of post-ERCP pancreatitis, pancreatic stents were placed. Rectal indomethacin, which had not yet become the standard of care for patients at high risk for post-ERCP pancreatitis [12], was not used. In spite of this, the rate of pancreatitis was not significantly different than a recent meta-analysis reporting post-ERCP pancreatitis rate of 10% in patients with SOD versus 4% in those without [13].

So where does this leave us? The EPISOD trial has substantiated our knowledge regarding the ineffectiveness of endoscopic sphincterotomy in patients with SOD Type III. The findings by Cotton *et al* should have major implications for the current paradigms of endoscopic intervention in post-cholecystectomy patients with ongoing pain (suspected SOD Type III) to the point that these patients should no longer be offered ERCP and sphincterotomy. It has also led to the questioning of whether or not SOD Type III should remain a clinical entity altogether. If such patients have normal liver enzymes, no evidence of biliary dilation and do not respond to sphincterotomy, can their pain be attributed to true sphincter dysfunction? Should it be considered biliary at all? Finally, the discordance between manometry results and response to sphincterotomy calls sphincter manometry itself into question as the gold or even reference [14] standard for the diagnosis of SOD. It is unreliable in SOD Type I and now appears to be futile in SOD Type III (and potentially Type II). To this end, the results of prior studies that used sphincter manometry as the standard by which non-invasive modalities (e.g. HIDA scans) were measured require re-evaluation. The Rome III consensus conference statement (2006) suggesting that patients with post-cholecystectomy pain should undergo

liver and pancreatic biochemical tests followed by ultrasound, MRCP, and then ERCP with sphincter manometry where appropriate [15] remains intact but the number of patients where this applies has been drastically reduced. We would urge physicians to carefully evaluate patients with “biliary pain” post-cholecystectomy and use the robust conclusions from this study to guide their practice and avoid further harm to this challenging group of patients.

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